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EXAMINER	
LUM, LEON YUN BON	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 12/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,647	VAN DER GREEF ET AL.	
	Examiner	Art Unit	
	Leon Y Lum	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20041202*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Objections

1. In the amendment filed 01 March 2002, claim 10 has been crossed-out, but there is not identification as to whether the instant claim has been cancelled. Since the entire claim has been crossed-out, it has been considered as having a cancelled status. In addition, claims 1-4 in the instant amendment do not have status identifiers. Since no line are crossed-out, claims 1-4 are considered to have original status. Applicant is reminded that proper claim status is required in any amendments to the claims.

2. Claim 7 is objected to because of the following informalities: it appears that the term "time-off flight" in line 5 should be "time-of-flight".

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3. In claim 1, line 3, the phrase "which method" is vague and confusing. The instant phrase appears to be missing at least one term that would render it less confusing.

4. In claim 1, lines 4 and 6, the phrase "controlled amount" is vague and indefinite. The specification does not define the phrase and it is unclear as to what would constitute a controlled amount. How is this different from an amount that is not controlled? What determines whether the amount is controlled?

5. In claim 1, line 4, the phrase "an effluent" is vague and indefinite. Does the instant phrase refer to the same "effluent" as in line 2, or are the two effluents different?

6. In claim 1, line 6, the phrase "the effluent" is vague and indefinite. Does the instant phrase refer to the effluent in line 2 or line 4, or to both?

7. In claims 2 and 4, line 6 of the claims, the term "suitable" is vague and indefinite. The specification does not define the term and it is unclear as to what type of limitation following the instant term would comprise the claimed invention.

With regards to claim 2, it is not clear what type of dissociation step (line 6) is considered suitable.

With regards to claim 4, it is not clear what type of carrier stream (line 6) is considered suitable.

8. In claim 2, lines 4-8, the phrase "and the bound ligands are detected after being separated from said ligand-affinity molecule complex in a suitable dissociation step, followed by separation of the ligand from the affinity molecule using a hollow-fiber module" is vague and confusing. Since the bound ligands are separated from the ligand-affinity molecule complex in lines 4-6, it is unclear as to how the ligands can be separated again using a hollow-fiber module in lines 7-8.

9. In claim 2, lines 9-10, the phrase "in which method the dissociation step" is vague and confusing. The instant phrase appears to be missing at least one term that would render it less confusing

10. In claim 2, line 10, the term "preferably" is vague and indefinite. The specification does not define the term and it is unclear as to whether the limitations following the instant term are part of the claimed invention since the instant term implies that other limitations may be claimed.

11. In claim 2, line 12, the term "and/or" is vague and indefinite. It is unclear whether the limitation following the instant term is included with the limitations preceding the instant term.

12. In claim 5, line 5, the term "optionally" is vague and indefinite. The specification does not define the term and it is unclear as to whether the limitations following the

instant term are part of the claimed invention since the instant term implies that other limitations may be claimed.

13. In claim 7, lines 2-3, the phrase "of the type" is vague and indefinite. The specification does not define the phrase and it is unclear whether the limitations following the instant term are part of the claimed invention since the phrase implies that the mass spectrometer (line 2) is similar to the limitations following the instant phrase, but could be a different limitation.

14. Claim 1 recites the limitation "the effluent" in line 2. There is insufficient antecedent basis for this limitation in the claim.

15. Claim 1 recites the limitation "the affinity molecules" in line 5. There is insufficient antecedent basis for this limitation in the claim. Line 4 of the instant claim recites "an affinity molecule", which is singular. However, the instant phrase is plural.

16. Claim 1 recites the limitation "the free and bound known ligands" in line 9. There is insufficient antecedent basis for this limitation in the claim.

17. Claims 2-4 recite the limitation "the ligand-affinity molecule complex" in lines 3-4 of claim 2, lines 2-3 of claim 3, and lines 3-4 of claim 4. There is insufficient antecedent basis for this limitation in the claim.

18. Claims 2-3 recites the limitation "the permeate stream" in line 8 of claim 2 and lines 4-5 of claim 3. There is insufficient antecedent basis for this limitation in the claim.

19. Claim 4 recites the limitation "the unbounded ligands" in line 5. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

21. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

22. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

23. Claims 1 and 5-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oosterkamp et al (Analytical Chemistry, 1994, vol. 66, pages 4295-4301) in view of Hsieh et al (Molecular Diversity, 1996, vol. 2, pages 189-196).

Oosterkamp et al reference teaches an on-line detection method comprising the addition of a controlled amount of an affinity molecule to an effluent of a fractionation step, whereby the affinity molecules bind analytes in the effluent, followed by the addition of a controlled amount of a known ligand capable of binding to the affinity molecule under suitable binding conditions, followed by a separation step to separate the free and bound known ligands, by disclosing that in a first step, affinity proteins such as antibodies or avidin are added to an LC effluent to react with ligands (analytes) eluting from the LC column and that in a second step, unbound affinity proteins react with an excess of labeled ligand to titrate the remaining free binding sites, wherein prior to detection of the labeled ligand/protein complex, free and bound label are separated (page 4295, abstract, lines 1-11).

However, Oosterkamp et al reference fails to teach the on-line coupling of the effluent of the fractionation to a mass spectrometer, wherein detection of either the free or bound known ligands is performed using the mass spectrometer.

Hsieh et al reference discloses combining chromatography with mass spectrometry to identify binders which interact with target biomolecules and study receptor-ligand interactions, in order to reduce the time for screening, ligand purification, characterization and identification, and maximizes the amount of information related to the ligand in a single experiment (page 191, left column, 1st paragraph, lines 1-18).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Oosterkamp et al, with the step of combining chromatography with mass spectrometry to identify binders which interact with target biomolecules and study receptor-ligand interactions, as taught by Hsieh et al, in order to reduce the time for screening, ligand purification, characterization and identification, and maximizes the amount of information related to the ligand in a single experiment. One of ordinary skill in the art at the time of the invention would have reasonable expectation of success in detecting binders and receptor-ligand interactions using mass spectrometry, as taught by Hsieh et al, in the method of Oosterkamp et al, since Oosterkamp et al teach chromatographic separation of complexed analytes, and the mass spectrometry taught by Hsieh et al can be coupled with chromatrographic separations and is able to detect biomolecule interactions.

With regards to claim 5, Oosterkamp et al reference teaches that the fractionation step is a liquid chromatography step, by disclosing that in a first step,

affinity proteins such as antibodies or avidin are added to an LC effluent to react with ligands (analytes) eluting from the LC column, as stated above (page 4295, abstract, lines 1-11).

With regards to claim 6, Oosterkamp et al reference teaches that the liquid chromatography separation step is a HPLC, by disclosing an HPLC column (Figure 1 and caption).

With regards to claim 7, Hsieh et al reference teaches that the mass spectrometer is time-of-flight, by disclosing that analyses is performed by matrix-assisted laser desorption/ionization time-of-flight (page 195, left column, 1st paragraph).

With regards to claim 8, Hsieh et al reference teaches that the mass spectrometer is set to detection ions of selected multiple m/z traces, by disclosing that with ESI mass spectrometry, the mass range for protein targets is 500-3000 m/z (page 195, left column, 1st full paragraph, lines 1-2).

With regards to claim 9, Hsieh et al reference teaches a compound detected, by disclosing a library of components and results from mass spectrometry (Table 1 and caption; and Figure 4 and caption).

24. Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Oosterkamp et al (Analytical Chemistry, 1994, vol. 66, pages 4295-4301) in view of Hsieh et al (Molecular Diversity, 1996, vol. 2, pages 189-196) as applied to claim 1 above, and further in view of Jurinke et al (US 6,303,309 B1) and Lutz et al (Journal of Chromatography, 1996, vol. 755, pages 179-187).

Oosterkamp et al reference has been disclosed above and additionally teaches that the separation step comprises the retention of the free ligand from the effluent using a restricted-access support, whereby the ligand-affinity molecule complex is permeated, by disclosing that a restricted-access reversed-phase support was placed in the carrier stream prior to the detector, wherein free fluorescein-biotin is retained at the hydrophobic inner surface of the pores and the avidin/biotin and avidin/fluorescein-biotin complexes are excluded from the pores and pass unretained to the detector (page 4298, left column, 1st full paragraph; and Figure 1 and caption). However, Oosterkamp et al reference fails to teach that the bound ligands are detected after being separated from said ligand-affinity molecule complex in a suitable dissociation step, followed by separation of the ligand from the affinity molecule using a hollow-fiber module, and directing the permeate stream containing the ligand to the mass spectrometer, in which method the dissociation step is preferably contacting with a high ionic strength.

Jurinke et al reference discloses decomplexation of biotin and biotin-binding compounds using ammonia, such as ammonium salt, in order to isolate biotin compounds for analysis using mass spectrometry, wherein biotin-binding compounds include avidin (column 3, lines 1-3; column 3, line 66 to column 4, line 7; column 5, lines 23-29; and column 6, lines 46-63).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Oosterkamp et al and Hsieh et al references with decomplexation of biotin and biotin-binding compounds using ammonia, such as ammonium salt, as taught by Jurinke et al, in order to isolate biotin compounds for

analysis using mass spectrometry. One of ordinary skill in the art at the time of the invention would have reasonable expectation of success in decomplexing biotin and biotoin-binding compounds using ammonia, as taught by Jurinke et al, in the methods of Oosterkamp et al and Hsieh et al, since Oosterkamp et al and Hsieh et al teach the complexing of avidin affinity proteins to unlabelled and labeled biotin analytes for the detection of biotin using mass spectrometry, and the decomplexation taught by Jurinke et al is performed on avidin-biotin complexes for the purpose of mass spectrometry.

However, Jurinke et al reference fails to teach the separation of the ligand from the affinity molecule using a hollow-fiber module

Lutz et al reference discloses that by introducing a membrane into the system with a cut-off between the size of a large antibody and a label so that free label passes the membrane freely, whereas the antibody-bound label will remain in the retentate stream (page 182, left column 1st paragraph, lines 3-9) and the permeate stream with free label is sent for detection (page 182, right column, 1st full paragraph, lines 1-6; and Figure 3 and caption), wherein separation of free and antibody-bound antigen is performed on a hollow-fibre module (page 181, left column , 2nd full paragraph), wherein free label is a labeled biotin (Figures 2-3 and captions), in order to perform a separation based solely on size and does not require regeneration (page 187, left column, 1st paragraph, lines 3-5).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Oosterkamp et al and Hsieh et al by introducing a membrane into the system with a cut-off between the size of a large antibody and a

label so that free label passes the membrane freely, whereas the antibody-bound label will remain in the retentate stream and the permeate stream with free label is sent for detection, wherein separation of free and antibody-bound antigen is performed on a hollow-fibre module, wherein free label is a labeled biotin, as taught by Lutz et al, in order to perform a separation based solely on size and does not require regeneration. One of ordinary skill in the art at the time of the invention would have reasonable expectation of success in applying hollow membrane fiber separation, as taught by Lutz et al, in the method of Oosterkamp et al and Hsieh et al, since Oosterkamp et al and Hsieh et al references teach the detection of biotin analytes, and the hollow fiber membrane, which retains larger particles, would retain bound complexes and allow smaller, labeled biotin to pass through to the detector. Since Jurinke et al reference teaches the decomplexation of avidin and biotin, the hollow fiber membrane would retain the larger avidin molecule and allow the permeation of biotin to the detector.

25. Claims 3-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oosterkamp et al (Analytical Chemistry, 1994, vol. 66, pages 4295-4301) in view of Hsieh et al (Molecular Diversity, 1996, vol. 2, pages 189-196) as applied to claim 1 above, and further in view of Lutz et al (Journal of Chromatography, 1996, vol. 755, pages 179-187).

Oosterkamp et al reference and Hsieh et al reference have been disclosed above and Oosterkamp et al reference additionally teaches that the separation step comprises the retention of the free ligand from the effluent using a restricted-access support,

whereby the ligand-affinity molecule complex is permeated, followed by the elution of the unbounded ligands from the restricted-access support using a suitable carrier stream (claim 4), by disclosing that a restricted-access reversed-phase support was placed in the carrier stream prior to the detector, wherein free fluorescein-biotin is retained at the hydrophobic inner surface of the pores and avidin/biotin and avidin/fluorescein-biotin complexes are excluded from the pores and pass unretained to the detector (page 4298, left column, 1st full paragraph; and Figure 1 and caption), and wherein after free fluorescein-biotin was retained on the support, the column was easily regenerated by rinsing with acetonitrile:water (page 4298, right column, 2nd paragraph). However, Oosterkamp et al reference fails to that the separation step comprises the retention of the ligand-affinity molecule complex from the effluent using a hollow-fiber module, whereby the free ligand is permeated, and the permeate stream with the free ligand is subsequently directed to the mass spectrometer (claim 3), and fails to teach the step of directing the eluted stream containing the free ligand to the mass spectrometer (claim 4).

Lutz et al reference discloses that by introducing a membrane into the system with a cut-off between the size of a large antibody and a label so that free label passes the membrane freely, whereas the antibody-bound label will remain in the retentate stream (page 182, left column 1st paragraph, lines 3-9) and the permeate stream with free label is sent for detection (page 182, right column, 1st full paragraph, lines 1-6; and Figure 3 and caption), wherein separation of free and antibody-bound antigen is performed on a hollow-fibre module (page 181, left column , 2nd full paragraph), in order

to perform a separation based solely on size and does not require regeneration (page 187, left column, 1st paragraph, lines 3-5).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Oosterkamp et al and Hsieh et al references by introducing a membrane into the system with a cut-off between the size of a large antibody and a label so that free label passes the membrane freely, whereas the antibody-bound label will remain in the retentate stream and the permeate stream with free label is sent for detection, wherein separation of free and antibody-bound antigen is performed on a hollow-fibre, as taught by Lutz et al, in order to perform a separation based solely on size and does not require regeneration. One of ordinary skill in the art at the time of the invention would have reasonable expectation of success in including a hollow-fiber membrane to retard the flow of complexed molecules, as taught by Lutz et al, in the method of Oosterkamp et al and Hsieh et al, since Oosterkamp et al and Hsieh et al teach sequential steps of adding affinity proteins and labels to an LC effluent, and further separating free and bound labels, and the hollow-fiber membrane of Lutz et al also separates free and bound labels after sequential steps of adding biomolecules to an LC effluent.

With regards to claim 4, Lutz et al reference discloses a permeate stream only containing free label and a retentate stream consisting bound label, in order to provide both free and antibody-bound label in separate streams that can be used for quantifying the original analyte concentration (page 182, right column, 1st full paragraph, lines 1-6; and Figure 3 and caption).

Conclusion

26. No claims are allowed.

27. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leon Y Lum whose telephone number is (571) 272-2878. The examiner can normally be reached on 8:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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